

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Pflaum et al. Art Unit: 1651
Appl. No: 09/600,566 Examiner: Irene Marx
International Filing Date: February 17, 1999 Docket No.: 2260/103
Invention: PROCESS FOR THE OBTAINING OF HMG-CoA REDUCTASE
INHIBITORS OF HIGH PURITY

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, Box 1450, Alexandria, VA, 22313-1450 on November 18, 2003.

Barbara J. Carter
Barbara J. Carter

Honorable Commissioner of Patents
Alexandria, VA 22313-1450

**DECLARATION OF ZLATKO PFLAUM, PH.D. IN SUPPORT OF
APPLICANTS' RESPONSE
[37 C.F.R. § 1.132]**

Dear Sir:

In response to the Office Action mailed August 18, 2003, in the above-reference matter, I hereby declare as follows:

1. My name is Zlatko Pflaum, M.Sc. I am one of the inventors of the subject matter of the above patent application and am an inventor on a number of other patents and pending patent applications involving HMG-CoA reductase inhibitors (Pflaum, Z., Turkalj, R.: Combined process for the purification of vancomycin hydrochloride US5853720, Pflaum, Z.: Process for the preparation of amorphous atorvastatin, US6613916, Pflaum, Z., Kerc, J.: Stabilized pharmaceutically effective composition and pharmaceutical formulation comprising the same, US6531507, Pflaum, Z.: Salts of HMG-CoA reductase inhibitors, US6583295, Pflaum, Z.: CRYSTALS OF THE

SODIUM SALT OF PRAVASTATIN, EP1200385A1, Pflaum, Z., Milivojevic, D.,
Senica, D.: PROCESS FOR THE OBTAINING OF HMG-CoA REDUCTASE
INHIBITORS OF HIGH PURITY, EP1054993A1, Pflaum, Z.: NEW SALTS OF HMG-
CoA REDUCTASE INHIBITORS, EP1114021A1). I am also an author or co-author of
a number of publications involving (KRALJ, B., ŽIGON, D., GRAHEK, Rok, HRIBAR
KIKELJ, Alenka, PFLAUM, Zlatko, MS/MS determination of some di and tripeptides.
V: *12th International Mass Spectrometry Conference, Amsterdam-Netherland, 26-30*
avgust, 1991, [S.I.]: [s.n.], 1991., RUČMAN, Rudolf, KOCJAN, Darko, GRAHEK, Rok,
MILIVOJEVIĆ, Dušan, PFLAUM, Zlatko. Isolation synthesis and structure
determination of 2-bromocryptine impurities. V: *TRISOC IV*. Trieste: University of
Trieste, 1991, p. 19., KRALJ, Bogdan, ŽIGON, D., GRAHEK, Rok, HRIBAR KIKELJ,
Alenka, PFLAUM, Zlatko. MS/MS determination of diastereoisomeric dipeptides. In:
Zbornik povzetkov. Ljubljana: Odbor za molekularne vede Sveta akademij Jugoslavije:
Slovensko kemijsko društvo – Spektroskopska sekacija, 1991, p.76., PFLAUM, Zlatko,
GRAHEK, Rok. Use of preparative hplc in garamine synthesis. In: *New achievements in*
chromatography : abstracts. Opatija: Croatian society for chemical engineering:
Croatian chemical society, 1992, p. LC-4., and GRAHEK, Rok, PFLAUM, Zlatko.
Preparative HPLC purification of pentapeptide analogue of thymopentin. In: *Symposium*
on modern chromatographic techniques : [abstracts] : Bled, 9-11 October, 1990,
[Ljubljana]: Ministry of Science and Technology of the Republic Slovenia, [1990], p.57.)
and have a strong background in organic chemistry synthesis, biosynthesis, purification,
analytics and structural analysis. My further credentials are set forth in my Curriculum
Vitae, which is attached as Exhibit A hereto.

2. I have read the action of August 18, 2003. This declaration is provided to clarify the record that someone of ordinary skill in the art would know and understand the terms "water-miscible or water-soluble" and "limited miscibility or limited solubility with water" and would be able to practice the claimed invention based on the application as written (enablement).

3. In Table 16 on page 469 of the Ullmann's Encyclopedia of Industrial Chemistry, Vol. A 24, (see attached Appendix B) data is provided on miscibility of solvents with water in wt % (weight %) at 20oC. From this table it is clear and concise that:

- some solvents have unlimited miscibility with water, since they freely dissolve in water (in Table 16 marked with the sign for "infinite"; and
- other solvents have limited miscibility with water and dissolve in it up to a certain wt % (as provided in table 16).

4. Among the solvents listed in Table 16 are the solvents with unlimited miscibility with water, e.g. methanol, ethanol, propanol, isopropyl alcohol, *tert*-butanol, ethylene glycol, methyl glycol, ethyl glycol, propyl glycol, butyl glycol, ethyl diglycol, methoxypropanol, methyldipropylene glycol, tetrahydrofuran, dioxane, acetone, diacetone alcohol, dimethylformamide and dimethyl sulfoxide.

5. Among the solvents listed in Table 16 are the solvents with limited miscibility with water, that is which dissolve in water in a certain amount in wt %, e.g. butanol, isobutanol, *sec*-butanol, hexanol, cyclohexanol, methylbenzyl alcohol, trimethylcyclohexanol, *sec*-butanolhexane, toluene, p-xylene, ethylbenzene, nitoethane, 1-nitopropane, 2-nitropropane, diethyl ether, dibutyl ether, methyl *tert*-butyl ether, methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, ethyl glycol

acetate, butyl glycol acetate, cyclohexyl acetate, butyl glycolate, propylene carbonate, methyl ethyl ketone, methyl isobutyl ketone, diisobutyl ketone, cyclohexanone, isophorone, trimethylcyclohexanone, hexane, dichloromethane, 1,1,1-trichloroethane, trichloroethylene and tetrachloroethylene.

6. Further, the terms limited and unlimited solubility are explained on pages 384-385 of the Comprehensive Dictionary of Physical Chemistry (see attached Appendix C). The term "unlimited solubility" is explained under the term "solubility" on page 384 as "Two substances can often be mixed in an arbitrary ratio - their mutual solubility is unlimited".

7. The term "limited solubility" is explained under the same term "solubility" on page 384 as "when the solubility is limited it is expressed by the composition of the corresponding saturated solution" and "when the solubility is limited, the composition of the corresponding saturated solution is expressed by an intensive quantity, e.g. by the mole fraction, mass fraction or by the concentration of the amount of substances, etc.".

8. In addition, the term miscibility is described in the Comprehensive Dictionary of Physical Chemistry as "mutual solubility" of two liquids with limited solubility, which form conjugate solutions (page 385).

9. Ullman's Encyclopedia and the Comprehensive Dictionary of Physical Chemistry are both incorporated by reference in the instant application. Moreover, on page 7, lines 7-14, of the description of the instant application it is disclosed that "In the meaning of the present invention, the term "water-miscible or water-soluble" shall refer to organic solvents which show essentially unlimited, preferably 100 % miscibility or solubility with water," and "the term "limited miscibility or solubility with water" shall also include water-immiscible or water-insoluble organic solvents." From this disclosure and the

cited references referred to as Appendices B and C, it is clear to a person with ordinary skill in the art which organic solvents are meant by the terms "water-miscible or water-soluble" organic solvent and which are organic solvents having "limited miscibility or solubility with water". Such solvents are also further exemplified on page 7 of the description of the instant application and also in the reference the Ullmann's Encyclopedia of Industrial Chemistry, Vol. A 24, cited in the description of the instant application and incorporated by reference.

10. In addition, common understanding by those having ordinary skill in the art is that solubilities of organic solvents in water are defined by the terms miscible with water (infinitely soluble) and immiscible with water (i.e., there is essentially no discernable or measureable amount of solubility). Organic solvents that cannot be characterized as either miscible or immiscible are understood to have limited miscibility with water. For example, in Chapter 6 (Solutions and Colloids), section 4 (Solubility), p. 181 of Bettelheim and March's General, Organic and Biological Chemistry, Fifth Addition (1998), Saunders College Publishing (attached as Appendix D), it states "For solutions of liquids in liquids, [s]ome liquids are essentially insoluble in other liquids (gasoline in water) and *others are soluble to a limit*. For example, 100 g of water dissolves about 4 g of ethyl ether (another liquid)." (See p. 181, emphasis added).

11. Later, in Chapter 12, (Alcohols, Phenols, Ethers and Halides), section 7 (Physical Properties), pp. 412-413 (attached as Appendix E), it states "... both alcohols and ethers are soluble in water, up to about three or four carbons, Alcohols and ethers of higher molecular weight, however, do not dissolve in water"

12. Another standard textbook, used to teach basic organic chemistry to many college students states that “Methanol, ethanol, both propyl alcohols, and tert-butyl alcohol are completely miscible in water. The remaining butyl alcohols have solubilities in water between 8.3 and 26.0 g/100 mL. ... Pentane, by contrast, is virtually insoluble in water.” See Solomon’s Organic Chemistry, Sixth Edition (1996), John Wiley & Sons, Inc., p. 419). (See Appendix F.) These two references are standard textbooks used to teach introductory chemistry in many colleges. As such, one having ordinary skill in the art would certainly understand at least these basic concepts of miscibility, immiscibility, infinite solubility, and limited miscibility or limited solubility with water to know that the terms define the solubilities of organic solvents by defining the two extremes of solubility – infinite solubility (water-miscible or water-soluble) and no solubility (immiscible or insoluble with water). It is not necessary to list solvents, or limits of solubility, for those skilled in the art would readily understand that the solvents falling between miscible with water and immiscible with water are those which have “limited miscibility or solubility with water.”

13. Nonetheless, Table 16 from Ullman’s Encyclopedia *does* list solvents having limited solubility, and the Comprehensive Dictionary of Physical Chemistry provides definitions for solubility, miscibility, and the concept of two substances having solubility that is limited. Finally, the application itself defines these terms.

14. Based on the cited references (Appendices B-F) and the description of the instant application it can be clearly understood that the organic solvents having limited miscibility or solubility with water are those which are not miscible and/or not soluble in

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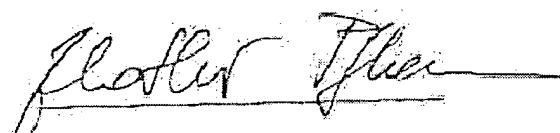
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water and those which are miscible and/or soluble with water up until to a certain amount or limit;

15. In summary, the knowledge generally available to those skilled in the art at the time of this application was such that the claims of the application, as written, including the phrases "limited-miscibility or limited-solubility" and "an organic solvent having limited-miscibility or limited-solubility with water" would be understood and are fully enabled. One skilled in the art would readily understand the limited number of organic solvents that have limited-miscibility or limited-solubility with water, and be able to practice the claimed invention without undue experimentation. Please consider these comments in conjunction with the response submitted herewith.

16. I hereby declare that all statements made herein are of my own knowledge and that all statements made on information and belief are true; and further that these statements are being made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



Zlatko Pflaum, M. Sc.

Dated: November 18, 2003.